REMARKS

Applicant hereby requests further consideration of the application in view of the amendments above and the comments that follow. This amendment is submitted in response to the Office Action mailed March 23, 2006 ("the Action"). Claims 1-35 were pending in the application and new Claims 36-39 have been added.

Allowable Subject Matter

Applicant acknowledges, with appreciation, the Examiner's statement that Claims 3, 6, 8-11, 18-20 and 35 would be allowable if rewritten in independent form including the limitations of the base claim and any intervening claims. Applicant has amended these claims above to place them in condition for allowance, which action is respectfully requested.

Claim 32

Claim 32 has been amended to obviate the informality with respect to the computer storage medium. Applicant respectfully requests that this rejection be withdrawn.

The Art Rejections

Claims 1, 2, 4, 5, 7, 12-17 and 21-34 stand rejected as being obvious over U.S. Patent No. 5,572,125 to Dunkel ("Dunkel") in view of U.S. Patent No. 6,721,583 to Durkin ("Durkin") and further in view of U.S. Patent No. 4,933,844 to Otvos ("Otvos"). More particularly, the Action alleges that Dunkel teaches measuring constituents in a subject with an NMR composite spectrum and other features and cites, *inter alia*, col. 13, lines 37-52. The Action concedes at p. 4 that Dunkel does not teach rotating the matrix and determining the concentrations of constituents in the sample or measuring the lipoproteins. However, the Action states that Durkin teaches rotating the matrix (col. 7, lines 29-39) and determining concentrations (col. 7, lines 29-39) and Otvos teaches measuring lipoproteins. The Action then concludes that it would have been obvious to modify Dunkel to include the teachings of Durkin and Otvos. Applicant respectfully disagrees.

Dunkel is directed to correction of various types of distortion of spectral and imaging data from sources including NMR (abstract). Dunkel proposes regression analysis of n-dimensional spectral and imaging data to correct signal drift, sample saturation, removal of phase, baseline and shim distortions and removal of unwanted signals from the data (abstract).

The Action states that Dunkel teaches generating a reduced design matrix (col. 27, line 65-col. 28, line 31) and computing weighting coefficients based on the design matrix (col. 14, lines 33-40), the reduced matrix and the composite matrix alleged "to deconvolve the spectral contribution" (col. 27, line 65-col. 28, line 31). Applicant respectfully disagrees.

For example, at col. 14, lines 33-40, Dunkel refers to the preceeding paragraph which states that deviations can be decreased by either adjusting the phase of the spectrum to fit the model or by adjusting model parameters to fit the data (col. 14, lines 20-33), and states that "this approach makes the well developed methods of regression analysis applicable to spectral correction and automated data analysis." Applicant was unable to find, *inter alia*, assessing constituent level or rotating a design matrix (conceded by the Action as missing from Dunkel), much less (a) selectively excluding data corresponding to certain of the principal components in the rotated design matrix, (b) generating a reduced design matrix based on the steps of rotating and excluding, or (c) computing regression fit weighting coefficients based on data in the reduced design matrix and the composite matrix for the plurality of individual constituents to determine the level of the selected constituents in the target sample.

Regarding the alleged teachings of the combined secondary references with Dunkel, Durkin is directed to the use of RAMAN spectroscopy using RAMAN spectra emitted from the eye for detecting molecular characteristics *in vivo*. One of skill in the art would not have been motivated to combine the teachings of these references in the manner alleged, as NMR and RAMAN spectroscopy are very different modalities with very different functional and operational requirements and because the statistical models used by the two references are

different. Indeed, Durkin (filed a number of years after Dunkel issued) proposes the use of PLS calibration model (col. 7, lines 50-61), not the claimed analysis methodology.

Independent Claims 1 and 23 are restated here for ease of discussion.

1. A method for determining the presence of and/or a measurement for a plurality of constituents in a composite signal extending about a spectrum of interest obtained from a target sample undergoing analysis, comprising:

generating a mathematical design matrix of constituent data comprising a plurality of selected individual mathematical constituent matrix data sets, each constituent matrix data set including constituent amplitude values of a respective spectrum lineshape of a selected independent parameter over a desired number of data points of a known reference sample that is generated by a predetermined analysis method;

generating a composite mathematical matrix comprising a data set of amplitude values of a composite spectrum lineshape of the selected independent parameter over the desired number of data points for a target sample undergoing analysis that is generated by the predetermined analysis method, the composite lineshape comprising spectral contributions from a plurality of the selected individual constituents included in the design matrix;

rotating the design matrix to provide a rotated design matrix of principal components;

selectively excluding data corresponding to certain of the principal components in the rotated design matrix;

generating a reduced design matrix based on the steps of rotating and excluding; and

computing regression fit weighting coefficients based on data in the reduced design matrix and the composite matrix for the plurality of individual constituents to determine levels of the selected constituents in the target sample.

23. A method of deconvolving a complex signal to evaluate an *in vitro* biosample, comprising:

(a) obtaining a plurality of individual NMR spectrum reference signals of selected target constituents of interest in an *in vitro* biosample;

(b) obtaining a composite NMR spectrum signal of the *in vitro* biosample taken from a subject for analysis, the composite signal including spectral contributions from a plurality of the individual target constituents of interest;

(c) generating a design matrix of individual data sets of the amplitude of the respective reference constituents in the NMR spectrum, the design

matrix having columns or rows of data that correspond to principal components that contribute to the spectral lineshape of the composite signal;

(d) rotating the design matrix;

(e) generating a reduced design matrix of principal component data by selectively excluding principal components that do not improve the estimation of the target constituents in the composite signal;

(f) deriving regression fit weighting coefficients for the selected target constituents in the composite signal;

(g) generating a calculated composite lineshape for the sample, the calculated lineshape being calculated based on the derived weighting coefficients of respective constituent reference spectrums of constituents potentially present in the sample, and

(h) determining the presence or absence of and/or the level or concentration of at least one selected constituent in the sample based on the calculated composite lineshape.

Applicant respectfully submits that Durkin, even allegedly properly combined with Dunkel, fails to teach or suggest at least the features emphasized above in independent Claims 1 and 23 or similar features in independent Claims 14, 32 and 33. Applicant respectfully submits that independent Claims 1, 14, 23, 32 and 33 are patentable for at least the emphasized features.

With respect to lipoproteins, Otvos teaches measuring lipoproteins using NMR signals while Dunkel describes how to correct signal information in automated analysis. Dunkel and Durkin, even combined with Otvos, fail to resolve the noted deficiencies and one of skill in the art would not have combined the references in the manner noted absent the teachings of the instant invention.

The other dependent claims are also patentable over the cited references for at least the reason that their respective base claims are patentable as well as for reciting inpendently patentable subject matter.

For example, the Action states that Dunkel teaches a sequential least squares restraint in a statistical regression analysis to force the defined weighting coefficients of target constituents of interest to be positive as recited in Claim 2 and points to col. 23, lines 66-col. 24, line 28 in support of this position. However, a closer reading of this text appears to note that constraints for "n" spectral points calculated with Equation 7: AxI =G, where A is the nxm design matrix, I intensity parameters and vector G represents spectral amplitudes.

Dunkel states that a trivial solution of the overlap model is obtained if only one intensity parameter is "real-valued" and all other components of the intensity vector I are zero (col. 24, lines 1-3). However, reading further, Dunkel states that "[i]nstead of solving this system of equations under the constraint that intensities be real-valued, Eq. 7 is split into two linear systems of equations, one for the real and one for the imaginary values" (col. 24, lines 53-56) emphasis added.

Applicant respectfully submits that Dunkel fails to teach or suggest forcing the weighting constituents to be positive as recited, for example, in Claim 2, or as recited in Claim 26, applying a sequential least squares analysis to restrain negative coefficients to zero until the target constituent or constituents of interest are non-negative.

Applicant respectfully submits that the claims are patentable over the cited references.

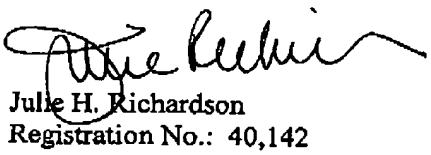
New Claims

Applicant has added new dependent Claims 36-39 in order to form a more complete claim set. The subject matter is supported by the specification, *see, e.g.*, p. 21. Entry and consideration of the claims is respectfully requested.

CONCLUSION

Accordingly, Applicant submits that the present application is in condition for allowance and the same is earnestly solicited. Should the Examiner have any matters outstanding of resolution, she is encouraged to telephone the undersigned at 919-854-1400 for expeditious handling.

Respectfully submitted,



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I hereby certify that this correspondence is being faxed to 571-273-8300 on June 23, 2006.

Joyce Pao